4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-D-2318]

Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." This guidance complements the 2019 draft guidance for industry entitled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (the 2019 Effectiveness draft guidance) and the 1998 guidance for industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (the 1998 Effectiveness guidance). Although FDA's evidentiary standard has not changed since 1998, there is a need for more Agency guidance to describe how one adequate and well-controlled clinical investigation and confirmatory evidence can be used to meet the substantial evidence requirement.

DATES: Submit either electronic or written comments on the draft guidance by "[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]" to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2023-D-2318 for "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly

viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001

New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Eithu Lwin, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6236, Silver Spring, MD 20993-0002, 301-796-0728; or Anne Taylor, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7242, Silver Spring, MD 20993-0002, 240-402-8113.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." This guidance complements the 2019 draft guidance entitled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" issued on December 20, 2019 (84 FR 70196) and the 1998 guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" issued on May 15, 1998 (63 FR 27093).

In 1962, Congress required for the first time that new drugs be shown to be effective as well as safe. A new drug's effectiveness must be established by substantial evidence. FDA has interpreted this substantial evidence requirement as generally requiring two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness.

In 1997, Congress amended section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(d)) to make clear that FDA may consider data from one adequate

and well-controlled investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data are sufficient to establish effectiveness. FDA issued the 1998 Effectiveness guidance in response to this legislative change. In 2019, the Agency concluded that more guidance was needed on the flexibility in the amount and type of evidence needed to meet the substantial evidence standard and issued the 2019 Effectiveness draft guidance, which discussed a number of approaches that can yield evidence that meets the statutory standard for substantial evidence.

Although both the 1998 Effectiveness guidance and the 2019 Effectiveness draft guidance provide examples of how a single adequate and well-controlled clinical investigation and confirmatory evidence can be used to support a marketing application, these guidances are not intended to provide a comprehensive discussion of meeting the substantial evidence standard based on one adequate and well-controlled clinical investigation and confirmatory evidence. Thus, there is a need for more Agency guidance to describe how one adequate and well-controlled clinical investigation and confirmatory evidence can be used to meet the substantial evidence requirement.

When one adequate and well-controlled clinical investigation and confirmatory evidence are considered together to assess effectiveness, the quality and quantity of the confirmatory evidence are also important considerations. Confirmatory evidence should be evidence generated from quality data derived from an appropriate source. The quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate.

This draft guidance describes these considerations in greater detail. It also provides examples of the types of evidence that could be considered confirmatory evidence that can be used with one adequate and well-controlled clinical investigation to demonstrate substantial evidence of effectiveness. Finally, the draft guidance includes recommendations for early

engagement with the Agency for sponsors who intend to establish substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

While this guidance contains no new collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521). The collections of information in 21 CFR parts 58, 312, 314, and 601 have been approved under OMB control numbers 0910-0119, 0910-0014, 0910-0001, and 0910-0338, respectively. In addition, the collections of information pertaining to FDA's guidance entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products" have been approved under OMB control number 0910-0001.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: September 14, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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